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**Factors influencing recruitment to a randomised placebo-controlled trial of oral  
naltrexone and extended release implant naltrexone: qualitative study**

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## **Declaration of interests**

CT has been supported by research grants from Mundipharma International Limited and Camurus AB to undertake qualitative research on opioid pharmacotherapy bio-delivery systems.

In the last 2 years, JN has received research grant support from Mundipharma International Limited and Camurus AB to undertake qualitative research on opioid pharmacotherapy bio-delivery systems.

JM is a clinical research psychologist and licensed cognitive behavioural psychotherapist. In the past three years, he declares research grants from the NHS England and the English Department of Health and Social Care (prison setting maintenance medication for opioid use disorder [OUD]); the National Institute for Health Research (NIHR; randomised controlled trial of depot naltrexone for OUD and a randomised controlled trial of acamprosate with behavioural intervention for alcohol use disorder), and the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Mental Health Foundation Trust (SLaM; randomised controlled trial of novel cognitive therapy for cocaine use disorder). He has part-time employment as Senior Academic Advisor for the Alcohol, Drugs, Tobacco and Justice Division, Health and Wellbeing Directorate, Public Health England (PHE) and is a clinical academic consultant for the US National Institute on Drug Abuse, Centre for Clinical Trials Network. JM declares an unrestricted research grant at IoPPN and SLaM from Indivior via Action on Addiction for a randomised controlled trial of tailored psychosocial intervention for non-response to ongoing methadone and buprenorphine treatment. He has received honoraria and travel support from Reckitt-Benckiser (2016; treatment of OUD) and PCM Scientific and Martindale for the Improving Outcomes in Treatment of Opioid Dependence conference (2015-2018; contributions and chairing). He holds no stocks in any company.

JS is a clinician and researcher who, through his university, has worked with various pharmaceutical companies to identify new or improved treatments and his employer (King's College London) has received grants, travel costs and/or consultancy payments; this has included consultations with companies who manufacture implant or depot naltrexone including, past 3 years, Martindale, Indivior, Mundipharma, Camurus and the university and clinical services have received supplies of study medications from companies including Braeburn/Camurus and also iGen (who provided the active and placebo naltrexone implants for the NEAT trial). For a fuller account, see JS's web-page at:

<http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx>

## **Abstract**

**Aims:** To understand the influences on recruitment to the Naltrexone Enhanced Addiction Treatment (NEAT) study, a randomised placebo-controlled trial of extended-release naltrexone (XR-NTX) implants for opioid use disorder (OUD), to learn lessons for the design and conduct of similar future research.

**Methods:** 29 face-to-face, semi-structured qualitative interviews were conducted with patients recruited to NEAT (n=6), patients not recruited (n=11), researchers who designed the trial (n=5), and staff who delivered the trial (n=7). The social marketing mix was used as a framework to guide the data analyses.

**Results:** Dimensions of the 7Ps of the social marketing mix - product, price, place, promotion, physical environment, people, and processes all influenced recruitment to the NEAT trial. Amongst other things, the potential to receive a naltrexone implant (product); the provision of transport passes and shopping vouchers (price); clear verbal explanations (promotion); familiarity of the trial setting (physical environment); and approachable, friendly and informative trial delivery staff (people) positively influenced recruitment. Whereas, wanting a less medical approach to recovery (product); the perceived time, physical, and psychological costs of taking part (price); service ideological opposition to naltrexone in recovery (place); inaccessible written information (promotion); the location and nature of the trial setting (physical environment); a lack of knowledge about implants (people); and the blind allocation and potential of placebo (processes) deterred people from joining the trial.

**Conclusions:** Qualitative research informed by the social marketing mix as an analytical framework yielded detailed insights into understanding the factors and circumstances that influenced recruitment to the NEAT trial. Our findings have implications for the planning and implementation of future addiction trials, especially trials of extended-release formulations.

**Keywords:** Clinical trial; naltrexone; opioid dependence; qualitative; social marketing; study recruitment

## **Abbreviations**

Extended-release naltrexone (XR-NTX)

Naltrexone (NTX)

Naltrexone Enhanced Addiction Treatment (NEAT)

Opioid use disorder (OUD)

Oral naltrexone NTX (O-NTX)

## **Highlights**

- Naltrexone (NTX) is an approved treatment for opioid use disorder (OUD)
- The evidence base for extended-release implantable naltrexone (XR-NTX) for OUD is in its infancy
- A clinical trial of oral and implant NTX in contrast to placebo struggled to recruit patients
- Qualitative interviews with patients and trial staff explored what influenced recruitment
- Social marketing offers an analytical framework to explore recruitment to clinical trials

## **1. Introduction**

Naltrexone (NTX) is an approved treatment for opioid use disorder (OUD) (Gowing et al., 2014; NICE, 2007; SAMHSA, 2018), a chronic, relapsing condition affecting millions of people worldwide (United Nations, 2018). Unlike full or partial opioid agonist medications such as methadone and buprenorphine, naltrexone is an antagonist which binds to the brain's receptors to block the effects of opioids. Consequently, NTX can be prescribed as a pharmacological relapse prevention strategy following opioid withdrawal.

Studies of the effectiveness of oral (tablet) NTX (O-NTX) for the treatment of OUD have been compromised by poor adherence to daily dosing and low retention rates in treatment (Adi et al., 2007; Minozzi et al., 2011). Issues with adherence to oral naltrexone prompted the development of long-acting extended-release injectable and implantable formulations (XR-NTX) (Friedmann et al., 2018; Goonoo et al., 2014; Jarvis et al., 2018). Designed to reduce the frequency of dosing by modifying the rate of release and absorption, these newer formulations are similar to each other in that they typically deliver therapeutic levels of naltrexone that last at least one, and up to seven, months (Jarvis et al., 2018). However, injectable and implantable NTX differ in that injectable NTX does not involve a surgical incision and insertion procedure and it cannot be removed after administration.

Injectable XR-NTX is now approved for the treatment of OUD in the United States (US) and Russia (Jarvis et al., 2018; SAMHSA, 2018). Implantable XR-NTX is only officially approved for use in Russia, but it is sometimes prescribed 'off label' under special circumstances, including in Australia and in a few private clinics in the United Kingdom (Krupitsky, Zvartau & Woody, 2010; Larney et al., 2014). Oral naltrexone is the only form of NTX licensed for use in the treatment of OUD in the UK and across Europe.

The evidence base for XR-NTX for OUD is developing (Friedmann et al., 2018). A Norwegian noninferiority trial concluded that injectable XR-NTX was as effective as daily oral

buprenorphine-naloxone in retaining patients in treatment, reducing the number of days injecting and craving for opioids, and reducing illicit drug use (Tanum et al., 2017). Additionally, a randomised controlled trial (RCT) in the US found it as safe and effective (Lee et al., 2018); although difficulties initiating inpatients to injectable XR-NTX in the study impacted on its ability to prevent opioid use or promote abstinence (Lee et al., 2018). This latter finding is supported by a systematic review which concluded that issues with initiation and premature discontinuation significantly limit the clinical utility of injectable XR-NTX (Jarvis et al., 2018). Further trials indicate that XR-NTX implants effectively reduce relapse to heroin use when compared with O-NTX (Hulse et al., 2009; Krupitsky et al., 2012) or placebo medication (Krupitsky et al., 2012; Tiihonen et al., 2012) or usual aftercare (Kunøe et al., 2009) and improve retention in treatment (Krupitsky et al., 2012; Tiihonen et al., 2012). However, another systematic review cautioned that the quality and quantity of evidence on the safety and efficacy of XR-NTX implants is limited and called for better evidence (Larney et al., 2014).

In recent years, researchers have begun to document their experiences of recruiting people with OUD to clinical trials, including the challenges faced (Demaret et al., 2014; Gartry et al., 2009; Melberg & Humphreys, 2010; Oviedo-Joekes et al., 2009; Oviedo-Joekes et al., 2015; Thomson et al., 2008). For example, the prospect of desirable treatments that are otherwise unavailable and the provision of incentives have encouraged recruitment to trials (Oviedo-Joekes et al., 2015; Thomson et al., 2008). Meanwhile, concerns about being allocated to placebo medication and other control conditions, personal medication preferences, and perceived excessive demands on participants have deterred participation (Demaret et al., 2014; Melberg & Humphreys, 2010; Thomson et al., 2008). Nevertheless, there is little empirical research into what influences participation in pharmacological addiction trials (Demaret et al., 2014; Neale et al., 2018a) and we lack detailed insights into *why* people agree or refuse to take part (Kunøe et al., 2009; Melberg & Humphreys, 2010; Oviedo-Joekes et al., 2015; Tiihonen et al., 2012).



Information on the recruitment of participants to XR-NTX implant trials is particularly scarce. Among the few NTX implant trials conducted to date, the desire to have active medication appears to have deterred participation in a trial of active and placebo implants (Hulse et al., 2009). Likewise, roughly 60% of 111 prisoners screened to take part in an open-label trial comparing XR-NTX implants and methadone treatment after release declined to participate, often as they wanted to maintain abstinence by relying on their own resources (Lobmaier et al., 2010b). Furthermore, 7 of the 23 prisoners randomised to XR-NTX implants did not initiate treatment as they wanted opioid maintenance treatment (Lobmaier et al., 2010a). Other trials involving active or placebo XR-NTX implants have also met refusals to take part both before and after randomisation (Kunøe et al., 2009; Tiihonen et al., 2012).

In 2010, the National Institute for Health Research (NIHR), Health Technology Assessment (HTA) Programme called for a three-arm randomised controlled double-dummy trial into sustained release naltrexone for opioid dependence (HTA, 2010) after their commissioned systematic review of oral naltrexone was inconclusive (Adi et al., 2007). Reflecting the requirements of the NIHR HTA call (HTA, 2010), the Naltrexone Enhanced Addiction Treatment (NEAT) trial was designed to explore the effectiveness of active XR-NTX implants and O-NTX in contrast to placebo medication in people with OUD seeking treatment to help them stay abstinent. Although the NIHR call for research did not request a pilot study, break-points were included in the full trial design to ensure that clinical and operational problems were assessed and rectified whenever possible in the early stages and the trial would be terminated if any difficulties could not be adequately addressed. Detailed information on the randomisation, clinical interventions, dosing regimens, and visit schedule is available elsewhere (Strang et al., in press). Key features of the trial are outlined in Box 1.

Box 1 here

The trial aimed to recruit 300 participants (100 to each intervention group). However, in spite of approaching 83 patients, only six patients were recruited in eleven months. The trial closed prematurely with the determination that recruitment to the study was not feasible in the current context.

We subsequently conducted a qualitative study to better understand the factors affecting recruitment and to learn lessons for the design and conduct of similar future research. This paper reports our findings, focusing on what influenced recruitment to the trial from the perspective of patients and staff. We draw on social marketing to frame our analyses, an approach which has previously been used to explore and promote recruitment in clinical trials (Dunleavy et al., 2018; Kobayashi et al., 2013; Nichols et al., 2004).

## **2. Methods**

Ethical approval for the qualitative study was obtained from the London Dulwich Research Ethics Committee in July 2017 (Ref: 14/LO/1615).

### *2.1 Sampling and recruitment*

Staff who delivered the trial provided the qualitative researcher (CT) with the details of the six people recruited to NEAT (referred to from herein as NEAT patients) and an anonymised list of 83 patients who had been approached about taking part in the trial, but who did not join the trial. CT identified 30 people not recruited to NEAT (referred to from herein as non-NEAT patients) from the list with different reasons for non-participation. Due to consent and data protection issues, trial delivery staff could only approach individuals who remained in methadone or buprenorphine treatment (n=14) to seek permission to pass their name and contact details to the researcher. Of the 14 patients still in treatment, three individuals could not be contacted. CT then contacted the six NEAT patients and 11 non-NEAT patients,

explained the study, and arranged interviews. CT also organised staff interviews with the researchers who designed the NEAT trial and the trial delivery staff.

## *2.2 Data collection*

In late 2017, CT conducted 29 face-to-face interviews with NEAT patients (n=6), non-NEAT patients (n=11), researchers who designed the NEAT trial (n=5), and NEAT trial delivery staff (n=7) (Tables 1 and 2). All participants provided written consent. Interviews took place in private and were audio recorded.

Tables 1 and 2 here

Separate topic guides were developed for patients and staff. Nonetheless, all were encouraged to discuss their views and experiences of the trial, including the screening and sign-up processes, information received about the trial, and what encouraged or discouraged them to take part in the trial. In addition, patients were questioned about their drug use and treatment histories; staff were asked how organisational factors affected recruitment.

Interviews with NEAT patients lasted between 63 and 92 minutes; non-NEAT patient interviews were shorter, between 36 and 65 minutes. The NEAT trial research staff and delivery staff interviews lasted between 52 and 104 minutes.

## *2.3 Analytical framework*

Social marketing is an approach aimed at changing or maintaining behaviour for the benefit of individuals and society (National Social Marketing Centre (NSMC), 2011). In social marketing, the marketing mix is used to gain a detailed understanding of the target market's attitudes, which can be altered to promote an intervention or service to achieve behavioural

change. The social marketing mix extends the commonly accepted '4Ps' of traditional marketing - product, price, place, and promotion to include other relevant components, as outlined in Box 2.

Box 2 here

#### *2.4 Data management and analyses*

All interviews were professionally transcribed verbatim. The transcripts were managed following the stages of Iterative Categorization (Neale, 2016). Firstly, CT developed separate patient and staff coding frames based on the topic guides and the interview discussions in the qualitative data software package, MAXQDA. The coding frames included separate codes for 'encouraged participation' and 'discouraged participation', each encompassing several sub-codes. Within each MAXQDA framework, CT then systematically coded the transcripts line-by-line by attributing portions of text to the relevant code/s.

After coding all transcripts, the 'encouraged participation' and 'discouraged participation' codes were exported from the patient and staff MAXQDA frameworks into separate Microsoft Word documents for inductive analyses. That is, CT read each patient Word document and methodically grouped and organised the data, keeping like with like. She repeated the exercise with the staff data. During the final stage of the analyses, CT mapped the groups of coded data to the 7 areas of the social marketing mix. Finally, the mapped data were compared for similarities and differences in the views and experiences of NEAT patients, non-NEAT patients, researchers, and delivery staff.

### **3. Findings**

Below we report the NEAT trial recruitment experiences, with verbatim quotations from interview participants to highlight key points.

### 3.1 Product

Patients discussed how features of the trial influenced decisions to take part in it. Individuals who wanted to cease illicit opiate use tended to be most interested in taking part as they believed that the trial offered a ‘*chance*’ to become opiate-free and move on with their lives.

*I don't want to take drugs, I want to live my life, I want to get back to work and be the person I once was. And at that stage I would have tried any trial or whatever going to help me do that. And it was just perfect timing really that I found out about the NEAT trial, and I put myself forward for it. (P17, female)*

Patients explained that the trial offered the potential for abstinence due to the antagonist properties of naltrexone to ‘*block*’ the effects of opioids. In particular, patients reported that the prospect of receiving an XR-NTX implant encouraged them to take part as they believed it would safeguard against opiate use. Thus, patients said that the trial provided a unique ‘*opportunity*,’ commenting that naltrexone implants were otherwise only available from a private clinic, at a high price.

*I wanted to get an implant because I thought that would be fantastic... it would guarantee me a three-month period of absolute total abstinence. (NP11, male)*

A second feature of the trial which encouraged a few patients to take part was the provision of weekly counselling with a keyworker. However, this also hindered recruitment as other patients worried that the counselling may be ‘*probing*’ and overly intrusive. Staff expressed disappointment that the offer of weekly counselling did not attract more recruits.

Concerns about the trial medication also discouraged patients from joining NEAT. Patients reported that they were largely unfamiliar with oral and implant NTX and they deliberated about taking part in the trial after they learned of possible side effects. They also commonly shared anxieties about the form of the trial medication. For example, patients expressed anxiety about the implant insertion, were concerned about the semi-permanence and possible complications of an implant, and worried that the trial implant was insufficiently tested.

*It worry me because I think about implant. I'm not saying it's wrong, I'm not saying it's bad, but we don't have no experience, nobody had done it, and they hope it's a good medication, and they hope that it will work... I didn't accept myself. (NP7, male)*

Other patients reported that they had not joined the trial because they wanted a less medical approach to recovery after spending many years on pharmacological treatment for OUD.

*I knew I didn't want to do it [enrol in the trial] straight away... I didn't want any more medication or anything else in my body. (NP8, male)*

In this way, trial delivery staff suggested the trial was at odds with how drug treatment services encouraged patients to develop resilience and self-efficacy in preparation for recovery.

### **3.1.1 Competition**

Staff believed that the limited prescription of NTX within the range of treatment services recruiting patients encouraged interest in the NEAT trial. Nevertheless, uptake to the trial faced competition from the 12-step model of addiction treatment. Patients who followed this

approach said that they favoured spirituality and mutual aid to support abstinence and recovery over pharmacological treatment.

*I've been in recovery for several years, and the fellowship and things like that have helped... they use more of a spiritual approach... that stuff is more useful to me than a tablet... The whole point of me being here is to get back my life, not a tablet to aid me in doing that, there's not a pill for such a thing. (NP5, male)*

The desire to use opioids also influenced recruitment to the trial. That is, some patients reported that the potential allocation to active NTX deterred them from enrolling in the trial as they did not want the effects of opiates to be 'blocked'.

*I thought, I don't know if I really want to take this thing just to block out everything... if something happens I might want to have a fix [use drugs]... I just knew I wasn't going to do it [enrol in the trial]. (NP9, male)*

Others explained that they were deterred from taking part as they worried that NTX might change how they experienced the effects of alcohol. Similarly, patient satisfaction with current methadone or buprenorphine maintenance or fear of losing the 'security' of this treatment competed with the trial and hindered uptake, as did pre-existing treatment plans to be drug and medication-free.

### 3.2 Price

Uptake to the NEAT trial was influenced by the perceived costs of taking part. Some patients believed that attending the clinic three times a week for 12 weeks for the trial would keep them occupied after detoxification, encouraging them to take part. More often however,

patients insisted that the number of visits would be '*inconvenient*' and '*a hassle*' when rebuilding their lives following abstinence.

*We had to go in there three times a week... I can handle once a week maybe, but three times a week is quite a big thing. (NP6, female)*

The time involved in attending clinic visits concerned patients with work or family commitments. Trial delivery staff also noted that screening was time consuming and involved '*intensive*' assessments and '*form-filling*'. Furthermore, patients worried about what might happen to their future contact with the service and their entitlement to receive social welfare benefits related to ill-health if they became abstinent and took part in the trial.

Patients also considered physical costs of taking part. Pain, scarring and possible site reactions or complications of being '*sliced*' or '*cut open*' to receive an implant commonly discouraged people from joining the trial, especially if they said that they were '*squeamish*' or if they reported negative experiences of medical procedures in the past.

*The implant involved having to cut someone... cut open their skin and put it in under their skin. And the patient didn't want this, put loads of patients off. (S7, researcher)*

Coupled with this, other costs which influenced patient uptake to the trial were more psychological in nature and stemmed from the blind allocation of treatment, the potential allocation to double placebo (including a dislike of the requirement to undergo a surgical procedure to receive a placebo implant), and the possibility of feeling '*trapped*' and with reduced choice over opioid use if allocated an active implant.



Nevertheless, those recruited to the trial considered that the benefits of taking part outweighed the perceived costs. For instance, even when considering the potential of allocation to double placebo, patients viewed the chance of allocation to active oral or implant naltrexone as favourable.

*You're two thirds likely to have something active, and one third likely to have... nothing active. So, either you've got one third possibility of having an active implant, one third possibility of having active pills, and one third possibility of having an inactive implant and inactive pills... I liked the odds... I wanted something to be real, because I knew that the drug did have an effect on heroin. (P13, male)*

Additionally, NEAT patients said that the provision of public transport passes and shopping vouchers to attend trial appointments minimised perceived financial costs and encouraged them to join the trial; some claimed that they would not have taken part without reimbursement.

*I was going to get paid for doing it... you get £25 a week vouchers... I don't think I would have done it for free. (P15, female)*

### 3.3 Place

Staff explained that the recent recommissioning of community addictions services locally had resulted in the loss of one of the three delivery settings before the trial had started and had caused significant changes in service provision in another of the locations. Staff outlined how their subsequent attempts to extend the trial to include further recruitment sites were unsuccessful, again related to local and sector-wide changes in the tendering, commissioning, and provision of services. Staff lamented how these issues undermined recruitment.

*There's carnage in the addictions field at the moment... contracts that are churning and changing so two of the centres never got off the ground... your hands are tied... you're already two thirds down... that's a more global reason, why we struggled to recruit. (S7, researcher)*

Although the NEAT trial was offered in various inpatient and outpatient services, staff reported that availability of the trial was influenced by a change of environment in the addictions field at the time of NEAT. Specifically, staff reported that the unexpected closure of inpatient detoxification units prevented the referral of potential patients to the trial and affected study recruitment. Furthermore, some referral services did not support the use of NTX in recovery on ideological grounds and this compounded recruitment problems.

*They [residential rehabilitation service] were quite clear that their whole philosophy is about teaching clients to manage emotions without drugs, and that you don't need drugs, and therefore naltrexone goes against that. (S4, delivery staff)*

Additionally, staff noted that referral to, and uptake of, the trial was hindered when service workers who could refer eligible patients to the trial were stretched with heavy workloads. Trial delivery staff reported that they could not always attend each service to encourage referrals, which limited recruitment.

### 3.4 Promotion

Patients reported that their first impressions of NEAT were of a professional and well-presented study. Underpinning these perceptions, patients observed that the trial was being conducted within reputable NHS treatment services by respected academics and clinicians. They commented that their confidence in, and understanding of, the trial was aided when

trial delivery staff provided them with clear verbal explanations and answered their questions.

*It was well versed, well presented, it was well spoken about. I mean it was confidently put across to me. No way did I feel like this person don't know what they're on about. (NP5, male)*

Delivery staff confirmed that the use of simple language and sketches when they explained the trial to potential patients aided comprehension and ultimately uptake. They noted that face-to-face communication was more successful in recruiting participants than promoting the trial by adverts. Yet trial delivery staff cautioned that promotion was compromised if other demands were made on their time.

*The drug service itself was going through a period of change, staff shortages, staff cuts... for the trial I don't think it was the best thing... I was getting pulled in a few different directions. (S9, delivery staff)*

In contrast, patients and delivery staff commonly complained that the trial information leaflet was too long, 'wordy,' and inaccessible, especially for patients with limited education or from low socio-economic groups. Patients with reading difficulties or whose first language was not English reported problems understanding the written information.

*I didn't actually read it, but it was about 4 or 5 bits of paper... I'm dyslexic. I sort of start reading something and I get bored. (P1, male)*

### 3.5 Physical environment

Staff believed the community addiction services were suitable locations for delivering the trial as they had the facilities to store trial medications, conduct the implant surgery, and monitor participants.

A few NEAT patients reported that the reputation and familiarity of the delivery service encouraged them to participate in the trial. More often, patients said that they did not want to attend a ‘*frontline*’ drug service when trying to distance themselves from drugs. They reported that they were wary about taking part in the trial as the service was located in a prolific drug-using area and they found the service environment ‘chaotic’. Most commonly, they feared that seeing drug users when attending trial appointments may trigger cravings to use heroin.

*Going to [drug service] is a nightmare... I start getting panicky, and I think who am I going to bump into in that waiting room? You know, most people in there are still heavily using, so if I'm clean, it's not somewhere I really want to go. (NP6, female)*

Proximity to the service also influenced recruitment – having further to travel and complications with transport put some patients off. Furthermore, patients from neighbouring services raised concerns about travelling to and attending an unfamiliar service when they anticipated feeling ‘*physically uncomfortable*’ and ‘*emotionally vulnerable*’ after detoxification.

### 3.6 People

Staff and patients highlighted that the qualities, availability, and knowledge of the NEAT trial delivery staff promoted recruitment to the trial. The trial researchers praised the dedication of the trial delivery staff. All staff believed that prior experience of working with people who use drugs enabled the delivery staff to form relationships when introducing the trial to potential participants.

*They hired amazing staff members to do it, who are so friendly and approachable, and that's really, really key. (S8, delivery staff)*

Similarly, patients reported that the those delivering the trial were approachable, friendly, informative, and supportive which helped them to ask questions about the trial and contemplate taking part. However, a patient who wanted to join the trial reported being dissuaded when a member of trial staff could not answer their question about NTX implants. Trial delivery staff confirmed that insufficient knowledge about implants sometimes influenced recruitment.

*We'd never worked with these implants... we didn't quite know what to expect. So it was very difficult, we couldn't reassure people, because we didn't know... when people ask you questions in a research trial, you want to have an answer... when you don't have that answer, that somehow changes the whole dynamics. (S2, delivery staff)*

Staff believed that the co-location of delivery staff within community addiction service encouraged relationships with the service staff, promoted referrals, and helped recruitment. For example, patients felt encouraged to trust the trial staff and consider the trial if a service keyworker with whom they had established relationships introduced the trial.

*Luckily, we were based in the same office as the opiate teams, we could just have conversations, sometimes someone would call me over to discuss a potential participant... Being based where we were was the best decision, I think in terms of having a presence and access to patients. (S9, delivery staff)*

Yet, patients sometimes struggled to inform trial delivery staff of decisions not to take part, for fear of disappointing them or their keyworkers. Occasionally, staff also suggested that recruitment was hampered when service keyworkers did not refer patients out of concern that the trial may threaten patient progress or stability in treatment.

### 3.7 Processes

NEAT trial patients welcomed having time to make an informed decision about taking part and to detoxify at their own pace. In addition, staff and patients felt that taking O-NTX in the pre-trial period helped patients to remain abstinent prior to joining the trial.

Trial patients understood there was a chance of getting double placebo but saw this as '*luck of the draw*' and accepted this as a common feature of trial design. On the other hand, patients said that the blind allocation of treatment and the potential allocation to placebo at a time of potential withdrawal and physical discomfort made them hesitant about taking part.

*I can understand why it [the trial] failed... if you said to me as someone coming off drugs, that you could be on this trial, and you're not going to know whether this drug is actually going to help you or not, or whether you're in a group that's even going to get it... how can you almost live your life, not knowing what, how you're going to feel tomorrow or the next day? (NP4, male)*

Compounding this, staff and patients frequently reported that the requirement to be completely abstinent from opioids for several days prior to joining the trial was a major barrier to recruitment. Concerns about feeling physically uncomfortable following detoxification also deterred some patients from taking part in the trial.

*It had to happen within a week after coming off the medication. I was quite wary that that was going to be a big difficulty... you are asking people to do something... that has an inbuilt kind of, unknown quantities in it at a period where they least want that kind of feeling. (NP10, male)*

Others who wanted to take part said that remaining abstinent was demanding and joining the trial was risked if they relapsed or if trial appointments were re-scheduled.

Trial delivery staff and patients also explained that intense screening processes deterred uptake to the trial, as patients often had to attend more than once to complete the required medical tests and assessment measures. Indeed, a patient who had detoxified for the trial changed his mind about taking part following ‘*extensive questionnaires*’ and ‘*intensive*’ screening.

Although trial delivery staff praised the flexibility and availability of the implant consultant, patients who completed screening occasionally reported that waiting for an implant appointment nearly prevented them from joining the trial. Likewise, those who designed the trial worried that the time between screening and consent to take part risked losing recruits.

*We then put you through a process of saying, ‘we’ll arrange an appointment for us to go over... the trial procedures, at the end of which you can give consent, at the end of which we then allow you a cooling off period, and if you then say yes, we’ll then book you in for the surgical minor ops procedure of having the implant’... Suddenly a week has gone... the critical week that you want to capture. (S6, researcher)*

#### **4. Discussion**

This qualitative study explored what influenced recruitment to a randomised controlled trial of the effectiveness of XR-NTX implants and O-NTX for OUD. We conducted the study to learn lessons after the NEAT trial closed prematurely after failing to recruit participants as planned.

As we only interviewed patients who remained in treatment for OUD, the findings may not transfer to people who had left treatment after being approached about the trial.

Furthermore, as interviews took place between 8 and 24 months after patients had been approached or involved in the trial, the accounts may be subject to recall bias.

Unlike existing reports of the experiences of recruiting people with OUD to clinical trials which tend to focus on the anecdotal perspectives of *either* staff *or* patients, a strength of our study is that we obtained and analysed first-hand accounts from staff *and* patients involved in the NEAT trial. That is, we interviewed all patients who were recruited to the trial and all staff involved in its design and delivery, including members of staff who had moved on after the trial. Obtaining these multiple perspectives helped to deepen and clarify our analyses and strengthened our confidence in the findings through triangulation (Silverman, 2000). A further strength of the study is our use of the social marketing mix as a conceptual framework to guide our analyses. By critically examining recruitment from the social marketing perspective, we identified how issues regarding the product, price, place, promotion, physical environment, people, and processes all overlapped to influence recruitment to the trial. As far as we are aware, this is the first use of the social marketing mix in an empirical addiction study.

Our analyses highlight how no single factor caused the recruitment difficulties experienced by the NEAT trial. Patients' numerous personal and practical issues competed with the trial and shaped their decisions about enrolment. For example, patients seeking abstinence from opiates were concerned that their resolve might be challenged if they met drug-using



associates when attending the drug treatment service for the trial (physical environment) and worried that employment opportunities might be compromised if newly acquired free-time was taken-up with trial appointments (price). Meanwhile, patients with less motivation to achieve abstinence tended to feel that the costs of taking part outweighed the potential benefits. For example, they saw reduced future contact with the drug treatment service and the potential loss of entitlement to health-related welfare (price) as possible negative consequences of relinquishing methadone or buprenorphine maintenance medications to join the trial.

Some of our findings, such as the 'burden' linked to the number and frequency of trial appointments and perceived excessive visit schedules (price), inaccessible written materials (promotion), and the blind allocation to treatment or potential allocation to double placebo (processes) resonate with the existing literature on factors that deter people who use opiates from participating in pharmacological trials (Demaret et al., 2014; Melberg & Humphreys, 2010; Thomson et al., 2008), including our own recent work (Neale et al., 2018a). Similarly, the prospect of an otherwise unavailable medication (product), the provision of travel passes and shopping vouchers (price), and hearing about the trial from a trusted service keyworker (people) reflect prior research on factors which encourage participation (Neale et al., 2018a; Oviedo-Joekes et al., 2015; Thomson et al., 2008). The influence of patient treatment preferences on recruitment decisions seems to reflect reports from existing naltrexone trials (Di Paola et al., 2014; Hulse et al., 2009; Kunøe et al., 2009; Lobmaier et al., 2010a; Lobmaier et al., 2010b; Tiihonen et al., 2012).

Our findings also identify issues which have been less well documented in the literature. For example, taking part in the trial was influenced by a desire for non-pharmacological approaches in recovery (product). At a service level, the recommissioning of treatment services (place) led to the loss of a trial delivery setting and contributed to difficulties in securing additional recruitment centres. Such findings may reflect the increasing emphasis

on recovery in UK drug policy, varying ideologies about the role of medication assisted treatment to support recovery, and changes in the commissioning and provision of drug treatment services.

Findings pertaining to patients' physical and psychological concerns about naltrexone implants (price) suggest a suspicion of implanted medication otherwise undetected in trials of XR-NTX implants (Hulse et al., 2009; Krupitsky et al., 2012; Kunøe et al., 2009; Lobmaier et al., 2010a; Tiihonen et al., 2012; Waal et al., 2006). Notably, these concerns do not appear to have influenced recruitment to trials of Probuphine®, a sustained-release buprenorphine implant (Ling et al., 2010; Rosenthal et al., 2013). Indeed, suspicion of implantable formulations seems to have received little attention outside of our own empirical qualitative research (Neale et al., 2018b), and appears to contrast with studies on the acceptability of injectable XR-NTX (Ahamad et al., 2015; Haase et al., 2016; Marcus et al., 2017; Marcus et al., 2018; Zaaier et al., 2016). Given that the market of long-acting extended-release medications for OUD is expanding (Barnwal et al., 2017; Hegde, Singh & Sarkar, 2013; Lorman, 2018; Sigmon & Bigelow, 2016; Walsh et al., 2017), attitudes to such medications require further investigation, not least in light of concerns regarding the uptake of Probuphine® implants in the US (Titan Pharmaceuticals, 2018).

To the best of our knowledge, this is the first empirical study of influences on recruitment to a clinical trial of an extended-release pharmacotherapy for OUD. Learning from our qualitative insights will therefore be most relevant to those planning and designing clinical trials of the effectiveness of extended-release formulations, as such trials will need to recruit large enough samples for meaningful analyses. For instance, the findings may help researchers to consider the duration of future trials given that extended-release medications are being developed to last up to 24 months (Reece, 2012), yet the three-month duration of the NEAT trial concerned patients. The findings may also help researchers consider how to balance the need to conduct rigorous scientific trials of extended-release medications with the need

for such trials to be ethical, safe, pragmatic, and attractive to the target population in real-world settings (Nunes et al., 2016).

Conducting detailed patient involvement and feasibility work is strongly advocated before any clinical trial commences to highlight any potential hurdles with recruitment and to identify the acceptability of a proposed intervention (Craig et al., 2008; O'Cathain et al., 2015). There is an abundance of guidance for researchers to inform the planning of clinical trials (see for example, Craig et al., 2008; O'Cathain et al., 2015), including our own recent checklist (Neale et al., 2018a). When developing interventions aimed at changing behaviours, social marketing prioritises the gathering of detailed knowledge of the target audience's needs, wants, and preferences while allowing for the consideration of trial-specific and local circumstances (NSMC, 2011). Social marketing has effectively influenced health behaviour in a range of areas, including alcohol and illicit drugs (Stead et al., 2007). When designing future real-world addiction trials, there may be benefit in the prospective use of both social marketing theory and existing clinical trial guidance alongside one another to understand issues influencing recruitment in order to yield the recruitment levels required.

## **Conclusions**

Qualitative research informed by the social marketing mix as an analytical framework yielded detailed insights into understanding the factors and circumstances that influenced recruitment to the NEAT trial. Our findings have implications for the planning and implementation of future addiction trials, especially trials of extended-release formulations.

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**Box 1: Key features of the Naltrexone Enhanced Addiction Treatment (NEAT) trial**

**Clinical trial registration:** ISRCTN95809946

**Design:** Double-blind, double-dummy, placebo-controlled randomised clinical trial.

**Target sample:** 300 patients with OUD who have completed opioid detoxification.

**Setting:** Available to patients from detoxification units, primary care, community addictions services, residential rehabilitation services, and prison drug services in three locations in England. Within each location, the trial was delivered in one designated community addictions service.

**Inclusion criteria:** 18 years or older; diagnosed with OUD as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM5); voluntarily seeking antagonist treatment for OUD; abstinent from opioids for at least seven days; able to provide written consent.

**Intervention:** Random allocation to one of three groups: 1) active XR-NTX implant and placebo O-NTX; 2) placebo XR-NTX and active O-NTX; 3) placebo XR-NTX and placebo O-NTX, each delivered over 12 weeks with weekly counselling. Specially produced iGen/Atral-Cipan implants (both active and placebo naltrexone) (Castanheira do Ribatejo, Portugal), performed by an experienced clinician at the community addictions service. Follow-up at 16, 24 and 36 weeks.

**Attendance:** Three clinic visits each week to collect trial medication, complete safety assessments, complete research measures, and receive weekly relapse-prevention oriented counselling with a keyworker to obtain measures of drug using status.

**Reimbursement:** Shopping vouchers (escalating payment schedule up to a maximum of £30 per week if patients attend all three trial clinic visits); provision of weekly public transport travel passes.

**Table 1: Patient characteristics**

	<b>NEAT patients (P) (n=6)</b>	<b>Non-NEAT patients (NP) (n=11)</b>	<b>Total (n=17)</b>
<b>Gender</b>			
Male	4	7	11
Female	2	4	6
<b>Age (years)</b>			
Mean (range)	39 (29-57)	43 (28-57)	42 (28-57)
<b>Ethnicity</b>			
White British	1	5	6
White Irish	0	1	1
White Other	1	2	3
Mixed White & Black Caribbean	3	0	3
Mixed White & Asian	1	0	1
Black British	0	2	2
Arab	0	1	1
<b>Current treatment</b>			
Buprenorphine	1	8	9
Methadone	1	2	3
Naltrexone	1	0	1
None	3	1	4

**Table 2: Staff characteristics**

	<b>NEAT researchers (n=5)</b>	<b>NEAT delivery staff (n=7)</b>	<b>Total (n=12)</b>
<b>Gender</b>			
Male	5	4	<b>9</b>
Female	0	3	<b>3</b>



**Box 2: The Social Marketing Mix** (Galli et al., 2014; NSMC, 2011)

**Product:** the intervention which is designed to meet the needs of the target audience, and competition to the intervention. In this instance, the NEAT trial is the product.

**Price:** the perceived financial, physical, or emotional cost/s of participating in the intervention.

**Place:** where the product (i.e. the NEAT trial) is made available to participants.

**Promotion:** the activities used to communicate information about the product (i.e. the NEAT trial) to the target audience.

**Physical environment:** where the product (i.e. the NEAT trial) is delivered.

**People:** staff who participants come into contact with about the product (i.e. the NEAT trial).

**Processes:** the actions required of people to participate.